

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
16 February 2006 (16.02.2006)

PCT

(10) International Publication Number  
**WO 2006/016376 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 311/58**

(21) International Application Number:  
PCT/IN2004/000241

(22) International Filing Date: 11 August 2004 (11.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US): **HETERO DRUGS LIMITED** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad, Andhrapradesh, Hyderabad 500018 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only):  
**PARTHASARADHI REDDY, bandi** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad, Andhrapradesh, Hyderabad 500018 (IN). **RATHNAKAR REDDY, kura** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500018 (IN). **RAJI REDDY, rapolu** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500018 (IN). **MURALIDHARA REDDY, dasari** [IN/IN]; Hetero Drugs Limited (R & D), Plot No. B-80 & 81, A.P.I.E., Balanagar, Hyderabad 500018 (IN). **SRINIVAS REDDY, itiyala** [IN/IN]; Hetero House, 8-3-166/7/1, Erragadda, Hyderabad, Andhrapradesh, Hyderabad 500 018 (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,

MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(U)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- of inventorship (Rule 4.17(iv)) for US only

**Published:**

- with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A NOVEL PROCESS FOR PREPARATION OF NEBIVOLOL INTERMEDIATES

(57) Abstract: The present invention relates to a process for separation of desired diastereomeric pair from a mixture of diastereomeric pairs thereby obtaining nebivolol intermediates. Thus, the mixture of (+)-[IS\*(R\*)]-6-fluoro-3,4-dihydro- $\alpha$ -[[[(phenylmethyl)amino]methyl]-2H-l-benzopyran-2-methanol, ranyl-2H-l-benzopyran and ethanol is heated to reflux temperature and stirred for 8 hours at the same temperature to obtain (±)-[2R\*[IS\*,5S\*(S\*)]]+[2R\*[IS\*,5R\*(R\*)]]-  $\alpha,\alpha'$ -[phenylmethyliminobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-l-benzopyran-2-methanol]. Then the reaction mass is cooled to 10°C, the pH is adjusted to 2 with HCl gas and stirred for 45 minutes at 25°C to 30°C. Then the separated solid is filtered and dried to give (+)-[2R\*[IS\*,5S\*(S\*)]]-  $\alpha,\alpha'$ -[phenylmethyliminobis(methylene)]bis[6-fluoro-3,4-dihydro-2H-l-benzopyran-2-methanol] hydrochloride salt, which can be converted into nebivolol.

WO 2006/016376 A1